## REMARKS

Claims 2 - 4 and 7 - 22 are pending in application, with claims 7 and 8 withdrawn from consideration as directed to non-elected subject matter. Claims 2 - 4, 9, 13, 15, 17 and 19 - 22 have been amended, claims 10 - 12 and 14 have been cancelled without prejudice or disclaimer herein, and claims 23-31 have been added. Accordingly, claims 2 - 4, 7 - 9, 13, and 15 – 31 will be pending in the application upon entry of the amendments presented herein.

The claims were amended to recite more clearly the instant invention, to make editorial changes and otherwise to expedite prosecution of the application. Support for the amendments can be found throughout the specification and claims as originally filed. Claims 23-31 were added to claim more fully the invention. Support for claims 23-31 can be found throughout the specification as originally filed. Specifically, support for new claims 23 and 24 can be found at least at pages 17 and 18 of the specification; support for new claim 25 can be found at least at pages 29-30 of the specification; support for new claim 26 can be found at least at page 26 of the specification; support for claims 27 ad 28 can be found at least at pages 18-19 of the specification; support for claims 29 and 30 can be found at least at pages 23 and 33 of the specification; and support for claim 31 can be found at least at page 39 of the specification. No new matter has been added.

In particular, claim 2 has been amended to recite "overactive bladder" and to recite "Vitamin $D_3$" compounds as a subclass of Vitamin D compounds. Support for the recitation of "overactive bladder" can be found at least, for example, in claim 12 as originally filed. Support for the recitation of "Vitamin $D_3$" can be found, at least, for example, in claims 17 - 22 as originally filed.

Additionally, claim 2 has been amended to exclude certain subgeneric formulae of various Vitamin $D_3$ compounds. Support for the two exclusionary provisos set forth in claim 2 as amended herein can be found in the specification at least, for example, at page 24, lines 1-21 and page 27, lines 6-18.

Applicant contends that the provisos recited in claim 2 do not introduce new matter. *See, In re Johnson*, 194 USPQ 187 (CCPA 1977).

In *In re Johnson*, the Requester/Patentee amended its generic claim to *exclude* certain species (or subgenuses) disclosed in a patent of another. In reversing the USPTO's rejection of those amended claims for allegedly lacking adequate written description, the Court said that

> The notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus and numerous species therewithin, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and thus has failed to satisfy the requirements of §112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute. . . . [T]he "written description" in the [parent application] specification supported the claims in the absence of the limitation, and that specification, having described the whole, necessarily described the part remaining. . . . **[U]nder these circumstances . . . appellants are merely excising the invention of another, to which they are not entitled, and are not creating an "artificial subgenus" or claiming "new matter."** [Emphasis added.]

In re Johnson, 194 USPQ at 196.

In the present application, the amendment made to claim 2 excises two subgeneric formulae of Vitamin $D_3$ compounds, which are clearly described in the specification at pages 21 and 27, from the generic class of Vitamin $D_3$ compounds, and does not create an artificial subgenus or add new matter. Thus, Applicant respectfully contends that the amendments presented herein are proper.

Amendment and cancellation of the claims are not to be construed as acquiescence to any objections/rejections set forth in the Office Action and were made solely to expedite prosecution without prejudice to pursuing the original subject matter of this application in a later filed application claiming benefit of the instant application, including without prejudice to any determination of equivalents of the claimed subject matter.

Applicant also requests rejoinder of the withdrawn claims of commensurate scope to the provisionally elected method of prevention and/or treatment claims upon allowance of claims directed to the elected invention.

***Rejection under 35 U.S.C. § 112, First Paragraph***

Claims 2 - 4 and 9 - 22 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description. It is alleged that "[t]here is no teaching or guidance how 'prevention' and 'treatment' of bladder dysfunction by such a large number of compounds would be treated successfully." Applicant respectfully disagrees and traverses the rejection.

However, without acquiescing to the rejection and in order to expedite prosecution, Applicant has amended claim 2 so that it is now directed to "overactive bladder" and "Vitamin $D_3$" compounds as a subclass of Vitamin D compounds. .

Regarding the term "preventing," Applicant notes that the MPEP (8th edition, Revision No. 6) states at section 2163.02, that written description can be demonstrated by the following:

> the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention...Possession may be shown in a variety of ways including description of an actual reduction to practice...

Applicant submits that working Examples 47 (pages 120-123) and 51 (pages 127-130) of the application as filed provide adequate written description that is commensurate in scope with the claims presented herein for preventing or treating overactive bladder.

Example 47 demonstrates the activity of calcitriol and a number of Vitamin $D_3$ analogs (see the table on pages 120-122) on the growth and function of bladder cells. Specifically, Applicant used an *in vitro* model of culturing human stromal bladder cells to prove that calcitriol and Vitamin $D_3$ have an effect on the growth and function of bladder cells.

Likewise, Example 51 describes a validated bladder outlet obstruction model that was used to evaluate the ability of vitamin $D_3$ analogs to control and treat bladder dysfunction. In particular, Compound A of Example 47 (1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol, recited in claim 19, which depends from claim 17) was evaluated to determine whether the compound at a dose

of 150 µg/kg/daily can prevent bladder hypertrophy and bladder dysfunction such as bladder overactivity.

As shown in Example 51, Compound A had a beneficial effect on bladder function:

> "This effect was evident in the normal bladder and is maintained in bladder outlet obstruction. In particular significant differences versus vehicle were observed in:
> -spontaneous non-voiding contraction frequency and amplitude (Figures 15 and 16);
> -residual urine (absent with the active compound, Figure 20);
> -micturition pressure (Figure 19).
> In addition a beneficial effect on bladder function has been confirmed in the *in vitro* tests:
> -K response;
> -response to EFS (Figure 21);
> -response to carbachol.
> Finally a slight decrease in bladder weight was observed with the vitamin $D_3$ analogue tested (Figure 16).
> These data demonstrate the use of vitamin D analogues (in the dose range from 50 µg to 300 µg - equivalent to approximately 0.725 to 5 µg/kg of body mass in humans) in the ***prevention and treatment of bladder dysfunction, such as overactive bladder***." [Example 51, page 130, lines 1-19. Emphasis added.]

Applicant respectfully submits that the specification, particularly when read in light of Examples 47 and 51, conveys with reasonable clarity to those skilled in the art that, as of the filing date of the application, Applicant was in possession of methods for preventing and treating overactive bladder by administering a Vitamin $D_3$ compound, as recited in the claims presented therein. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

***Rejection under 35 U.S.C. § 112, Second Paragraph***

Claims 2 and 3 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, it is alleged that there are no steps for obtaining or synthesizing a vitamin D compounds and the claims are open ended. Applicant respectfully disagrees and traverses the rejection.

As presented herein claim 3 is directed to the method of claim 2, "which further comprises the step of obtaining or synthesizing the Vitamin $D_3$ compound." This claim was drafted specifically for the purpose of optimizing enforcement of the patent. In other words, the person who practices the method of claim 2 must obtain the Vitamin $D_3$ compound or synthesize it in order to practice the method. If the person obtains the compound, he/she must purchase it or otherwise acquire it from a third party. In providing the compound to the person who practices the claimed method, the third party is inducing infringement. The acts of obtaining (purchasing or otherwise acquiring) and synthesizing are activities that are easily traced, thereby facilitating enforcement of the claims.

One of ordinary skill in the art will readily appreciate the meaning of "obtaining" in this context. Furthermore, the application describes on pages 49-52 and in working Examples 1-46 the syntheses of the vitamin $D_3$ compounds of the invention. Pages 49-52 of the application also provide numerous literature references and published patents and patent applications describing the syntheses of various compounds of the invention, and those references have been incorporated into the application by reference. Applicant submits that claims 2 and 3 are sufficiently definite within the meaning of the second paragraph of 35 U.S.C. §112 and, therefore, respectfully requests reconsideration and withdrawal of the rejection.

***Double Patenting Rejection***

Claims 2 - 4 and 9 - 19 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting over claims 1 - 6, 8, 9, 11, 12, 15, 23, 24, 31 and 32 of application Ser. No. 10/903,211 (now U.S. Patent 7,332,482, the "482 patent"). (In view of the issuance of U.S. Patent 7,332,482, Applicant assumes that the obviousness-type double patenting rejection is no longer provisional.) It is alleged that the claims of the '482 patent are drawn to methods of treating benign prostatic hyperplasia (BPH) using 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol and, therefore, the claims of the '482 patent and the claims of the application, drawn to preventing or treating bladder dysfunciton, are not patentably distinct. Applicant respectfully disagrees and traverses the rejection.

The claims of the '482 patent are directed to methods for treating benign prostatic hyperplasia (BPH) using 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol. In contrast, the claims as amended herein are directed to a method for preventing or treating overactive bladder using Vitamin $D_3$ compounds.

Applicant submits that the claims of the application are not obvious over the claims of the '482 patent because the claims of the '482 patent do not provide any teaching, suggestion or motivation to use Vitamin $D_3$ compounds for the prevention or treatment of overactive bladder, nor do they provide any reasonable expectation that such compounds would successfully prevent or treat overactive bladder.

BPH is characterized by an enlarged prostate gland (hence a disorder that affects only men), which can cause mild to moderate problems of urinating due to squeezing or partial blocking of the urethra. In contrast, overactive bladder is a disorder that affects men and women. The urinating problems associated with overactive bladder, which include urinary urgency, frequency and nocturia, are caused by repeated and uncontrolled bladder contractions. Although the symptoms of both disorders relate to urinating problems, one of ordinary skill in the art would not consider treatment of overactive bladder to be obvious in view of BPH because the underlying causes (*i.e.*, enlarged prostate gland for BPH and repeated and uncontrolled bladder contractions for overactive bladder) are distinct and because BPH only affects men whereas overactive bladder affects both men and women.

Applicant submits that the claims presented herein are not obvious in view of the claims of the '482 patent. Therefore, Applicant respectfully requests reconsideration and withdrawal of the rejection.

***Rejection under 35 U.S.C. § 103***

Claims 2-4 and 9-21 are rejected under 35 U.S.C. § 103 as being unpatentable over Batcho (US 5,939,408), Bishop, *et al.* WO 98/29123 ("Bishop I") and Bishop, *et al.* US 6,566,353 ("Bishop II"). It is alleged that Batcho, Bishop I and Bishop II teach the use of a vitamin D compound to treat BPH. Specifically, it is alleged that Batcho

teaches the use of 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol to treat neoplastic disease, Bishop I teaches methods of treating prostatic disease, including prostate cancer and prostate hyperplasia, using vitamin D compounds, and Bishop II teaches methods of treating hypercalcemia using a vitamin D compound. It is then alleged that it would have been obvious to one of ordinary skill in the art to use 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol to treat prostate hyperplasia or bladder cancer, upon a reading of all three references in combination. Applicant respectfully disagrees and traverses the rejection.

As noted above, the claims as amended herein are directed to a method for preventing or treating overactive bladder using Vitamin $D_3$ compounds. In contrast, Batcho teaches the synthesis of various vitamin D compounds and the use of such compounds in treating hyperproliferative skin diseases or neoplastic disease. Batcho does not provide any teaching or suggestion to treat bladder dysfunction, and clearly does not teach or suggest the prevention or treatment of overactive bladder. Moreover, hyperproliferative skin diseases and neoplastic disease, and the underlying causes of such diseases, are so distinct from overactive bladder and its underlying causes that one of ordinary skill in the art would not be motivated, based on the teachings of Batcho, to use the compounds disclosed in Batcho to treat overactive bladder.

Bishop I teaches the use of various vitamin D compounds to treat prostatic disorders such as prostate cancer and prostatic hyperplasia. By definition, prostatic disorders such as prostate cancer and prostatic hyperplasia are necessarily related to the prostate gland and are characterized by an enlarged prostate gland (hence a disorder that affects only men), which can cause problems of urinating due to squeezing or partial blocking of the urethra.

In contrast, overactive bladder is a disorder that affects men and women. The urinating problems associated with overactive bladder, which include urinary urgency, frequency and nocturia, are caused by repeated and uncontrolled bladder contractions.

However, notwithstanding the similarity in symptoms, one of ordinary skill in the art would not consider treatment of overactive bladder to be obvious in view of treatment of prostate cancer and prostatic hyperplasia because the underlying causes (*i.e.*, enlarged prostate gland for prostate cancer and prostatic hyperplasia and repeated and uncontrolled bladder contractions for overactive bladder) are distinct and because prostate cancer and prostatic hyperplasia only affect men whereas overactive bladder affects both men and women.

Moreover, Bishop I is largely directed to the treatment of cancer. In contrast, the claims of the application are not directed to cancer treatment (see page 6 of the application, line 33).

Bishop II discloses a method of treating hypercalcemia associated with malignant or neoplastic cells by treating the cells with a Vitamin D compound where the cells are bladder cancer cells. However, Bishop II neither teaches nor suggest treating overactive bladder. Moreover, the types of bladder dysfunction contemplated by the invention, such as overactive bladder, exclude bladder cancer (see page 6 of the application, line 33).

Batcho, Bishop I and Bishop II, whether alone or in combination, do not disclose "overactive bladder," and further do not teach or suggest that vitamin D3 compounds can be used to prevent or treat overactive bladder. Thus, even if there were some motivation to combine the references, the combination does not provide all of elements of the Applicant's claims as presented herein.

Applicant submits that claims presented herein are patentable under 35 U.S.C. § 103 over Batcho, Bishop I and Bishop II and respectfully requests reconsideration and withdrawal of the rejection.

***Rejection under 35 U.S.C. § 103***

Claims 2-4 and 9-22 are rejected under 35 U.S.C. § 103 as being unpatentable over Batcho (US 5,939,408), in view of Crescioli (J. Clinical Endocrinology & Metabolism). It is alleged that Batcho teaches 1-alpha-fluoro-25-hydroxy-16,23E-diene-26,27-bishomo-20-epi-cholecalciferol and its use to treat neoplastic disease. It

is alleged that Crescioli teaches a vitamin D compound to treat BPH. It is then alleged that it would have been obvious to one of ordinary skill in the art to select the

compound of Batcho to use in the method of treating BPH as disclosed in Crescioli. Applicant respectfully disagrees and traverses the rejection.

Claim 2 has been amended to recite a method of preventing or treating overactive bladder using a Vitamin $D_3$ compound. In contrast, Batcho teaches the synthesis of various vitamin D compounds and the use of such compounds in treating hyperproliferative skin diseases or neoplastic disease. Batcho does not provide any teaching or suggestion to treat bladder dysfunction, and clearly does not teach or suggest the prevention or treatment of overactive bladder. Moreover, hyperproliferative skin diseases and neoplastic disease, and the underlying causes of such diseases, are so distinct from overactive bladder and its underlying causes that one of ordinary skill in the art would not be motivated, based on the teachings of Batcho, to use the compounds disclosed in Batcho to treat overactive bladder.

Crescioli teaches that 1,25-dihydroxy-16-ene-23-yne D3 affected BPH cell proliferation and counteracted the activity of certain growth factors of BPH cells. The investigators then conclude that 1,25-dihydroxy-16-ene-23-yne D3 would be effective in treating BPH. Crescioli neither teaches nor suggests treatment of overactive bladder.

As note above, BPH is characterized by an enlarged prostate gland (hence a disorder that affects only men), which can cause mild to moderate problems of urinating due to squeezing or partial blocking of the urethra. In contrast, overactive bladder, is a disorder that affects men and women. The urinating problems associated with overactive bladder, which include urinary urgency, frequency and nocturia, are caused by repeated and uncontrolled bladder contractions. Although the symptoms of both disorders relate to urinating problems, one of ordinary skill in the art would not consider treatment of overactive bladder to be obvious in view of BPH because the underlying causes (*i.e.*, enlarged prostate gland for BPH and repeated and uncontrolled bladder contractions for overactive bladder) are distinct and because BPH only affects men whereas overactive bladder affects both men and women.

There is nothing in either Batcho or Crescioli that would motivate one of ordinary skill in the art to modify the teachings of the references or to combine the references to arrive at the invention as claimed herein. Moreover, even if there were some motivation to combine the references, the combination would not provide all of elements of the Applicant's claims as presented herein because neither reference teaches or suggests treatment of overactive bladder.

Applicant submits that claims presented herein are patentable under 35 U.S.C. § 103 over Batcho and Crescioli and respectfully requests reconsideration and withdrawal of the rejection.

## CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully request favorable reconsideration and withdrawal of all rejections, and allowance of this application with claims 2 - 4, 7 - 9, 13 and 15 - 31 presented herein. If a telephone conversation with Applicant's representative would help expedite the prosecution of the application, Applicant urges the Examiner to call the undersigned at (617) 517-5509.

Applicant authorizes the Director to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to Deposit Account No. 04-1105, under Order No. 62138US(49949).

Respectfully submitted,

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